REMARKS/ARGUMENTS

Status of the Restriction

The Examiner has reconsidered the Restriction Requirement mailed October 6, 2006 and has decided to withdraw the species election requirement and fully examine claims 1-22. Applicant acknowledges the withdrawal of the species election requirement and appreciates the Examiner's reconsideration of this issue.

Status of the Claims

Claims 1-22 were rejected. The subject matter of claims 2 and 6 has been incorporated into claims 1 and 5, respectively, to expedite prosecution, and, therefore, claims 2 and 6 have been canceled. Claims 9 and 11-22 have also been canceled to further prosecution. Applicant expressly reserves the right to file a continuation or divisional application or to take other such appropriate action to seek protection of the canceled claims.

Independent claims 1 and 5 have been amended to recite that the immune system disorder is selected from the group consisting of HIV infection, AIDS, and adenosine deaminase deficiency-dependent severe immunodeficiency disease (ADA SCID). New claims 23-28 have also been added. Support for the claim amendments and the newly submitted claims can be found in the specification and claims as originally filed. No new matter has been added by way of the claim amendments or the submission of new claims 23-28.

Claims 1, 3-5, 7-10, and 23-28 are now pending in the present application. Reexamination and reconsideration of these claims are respectfully requested in view of the claim amendments and the following remarks. The Examiner's comments in the Office Action are addressed below in the order set forth therein.

Information Disclosure Statement

The Information Disclosure Statement filed on March 24, 2006 has not been fully considered because Applicant failed to provide the Examiner with a copy of Lambrecht *et al.* (1996) *J. Autonomic Pharmacol.* 16:341-344 (i.e., citation no. 4). Applicant appreciates the

Examiner pointing out this error and has submitted herewith in the Appendix a copy of citation no. 4 and a clean copy of the Form 1449 previously filed. Applicant requests that the Examiner consider this reference and return the initialed Form 1449 to Applicant with the next communication from the Office.

The Rejection of the Claims Under 35 U.S.C. § 112, Second Paragraph, Should Be Withdrawn

Claims 2 and 6 were rejected under 35 U.S.C. § 112, second paragraph, as failing to particularly point out and distinctly claims the subject which Applicant regards as the invention. In particular, the Examiner has asserted that original claims 2 and 6 are indefinite for reference to HIV infection as an "immune system disorder." As indicated above, the subject matter of claims 2 and 6 has been incorporated into claims 1 and 5, respectively, and original claims 2 and 6 have been canceled. The present rejection is addressed insofar as it may apply to amended claims 1 and 5.

The Examiner is respectfully reminded that Applicants act as their own lexicographers and claim terms are to be interpreted in view of the specification. See MPEP 2173.01. An "immune system disorder" is defined in the instant application to *include* HIV infection. See, for example, page 9, lines 22-26. Accordingly, while the Examiner may disagree that the term "immune system disorder" encompasses HIV infection based on his own definition of this term, "immune system disorder" is expressly defined in the present specification to include HIV infection. Applicant further notes that "[w]hen the specification states the meaning that a term in the claim is intended to have, the claim is [to be] examined using that meaning." See MPEP 2173.05(b) and *In re Zletz*, 893 F.2d 319 (Fed. Cir. 1989). Therefore, in light of the above remarks, Applicant respectfully requests that the rejection for indefiniteness of the claims be withdrawn.

The Rejection of the Claims Under 35 U.S.C. § 112, First Paragraph, Should Be Withdrawn

Enablement

Claims 1-22 were rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to enable one skilled in the art

to make or use the invention. This rejection is respectfully traversed with respect to the amended claims.

Independent claims 1 and 5 as originally filed were directed to a method for treating an immune system disorder in a subject in need of such treatment comprising administering to the subject a compound selected from the group consisting of A_1 adenosine receptor antagonists, P_{2X} purinoceptor antagonists, and a combination of at least one A_1 adenosine receptor antagonist and at least one P_{2X} purinoceptor antagonist, wherein the compound(s) are administered in an amount effective to treat the immune system disorder. The Examiner concludes that the specification is not enabling throughout the scope of the claims. Applicant respectfully disagrees with the Examiner's conclusions with respect to the amended claims.

The Examiner is respectfully reminded that to satisfy the enablement requirement Applicants need not demonstrate that every A_1 adenosine receptor antagonist, P_{2X} purinoceptor antagonist, or combination thereof encompassed by the claims could be used to successfully practice the invention, such that no experimentation would be required. According to the applicable case law, the appropriate test of enablement is not whether experimentation is necessary to make and use an invention, but rather if experimentation is necessary, whether it is undue. *In re Angstadt*, 198 USPQ 214, 219 (C.C.P.A. 1976). Furthermore, a considerable amount of experimentation is permissible if it is merely routine or if the specification provides a reasonable amount of guidance in which the experimentation should proceed. *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988).

The test of whether an invention requires undue experimentation is not based on a single factor, but rather is a conclusion reached by weighing many factors. *Id.* at 1404. Factors to be considered in determining whether undue experimentation is required include the quantity of experimentation necessary, the amount of guidance provided in the specification, the presence of working examples of the invention in the application, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability in the art, and the breadth of the claimed invention. *Id.* Accordingly, the holding of *Wands* does not require that Applicants provide as working examples every A_1 adenosine receptor antagonist, P_{2X} purinoceptor antagonist, or combination thereof that can be used to practice the invention. Rather, *Wands* sets

out factors to be considered in determining whether undue experimentation is required to make and use the invention.

The Examiner concludes that the specification is not enabling throughout the scope of the claims because the breadth of the claims "is excessive and encompasses 'any immune system' disorder" (see page 3, point 1). Although Applicant maintains that the claims as originally filed are fully enabled, as noted above, independent claims 1 and 5 have been amended and now expressly recite that the immune system disorder is HIV infection, AIDS, or adenosine deaminase deficiency-dependent severe immunodeficiency disease (ADA SCID). Accordingly, Applicant respectfully submits that the Examiner's enablement rejection set forth at point 1 has been obviated and should be withdrawn.

The Examiner further asserts that original claims 1-22 fail to satisfy the requirements of enablement under 35 U.S.C. § 112, first paragraph, because Applicant and the prior art have not demonstrated that the compounds recited in the claims would be reasonably anticipated to be effective in the prevention or treatment of HIV infection, AIDS, or adenosine deaminase deficiency-dependent severe immunodeficiency disease (ADA SCID). See points 2, 3, 6, and 7 of the instant Office Action. We disagree with the Examiner's conclusions on this point.

Previous research implicates A_1 adenosine receptors and P_{2X} purinoceptors in immunodeficiency diseases such as HIV infection, AIDS, and ADA SCID. A_1 adenosine receptors are expressed on human immune cells and antigen-presenting cells (APCs), including dendritic cells, monocytes, macrophages, lymphocytes, peripheral blood mononuclear cells, and neutrophils. Both adenosine and HIV infection lead to a decrease in expression of CD4 on the surface of T cells, and HIV-mediated decreases in CD4 expression are considered to be an adenosine receptor-related phenomenon. See Sarzynska (2003) *J. Biomol. Structure Dyn.* 20:849; and Sipka *et al.* (1988) *Acta Biochim. Biophys. Hung.* 23:75-82. In addition, HIV contains a polyadenylated 3' end that can interact with adenosine receptors on human leukocytes. *Id.* Entry of HIV into target cells is dependent on interaction of a viral envelope glycoprotein with CD4 and one or more G protein-coupled receptors (e.g., adenosine receptors). See McElhinny *et al.* (1995) *J. Virol.* 69:1500-1509; Asin *et al.* (1999) *J. Virol.* 73:3893-3903; and Unutmaz *et al.* (1998) *Semin. Immunol.* 10:225-236.

Moreover, it is well known in the art that HIV replicates in the absence of cytotoxicity, escapes surveillance by the immune system, and spreads via cell-to-cell contact. Researchers further postulate that persistence of HIV in human macrophages is dependent on NF-κB expression. *Id.* Lipopolysaccharide (LPS), which binds to and activates A_1 adenosine receptors (Wilson and Batra (2002) *J. Endotoxin Res.* 8:263-271), activates nuclear translocation of NF-κB, stimulates expression of HIV in monocytes and macrophages, induces HIV expression in transgenic mice, and increases expression of HIV receptors on CD4+ T cells. See Sweet and Hume (1996) J. *Leuk. Biol.* 60:8-26; Pomerantz *et al.* (1990) *J. Exp. Med.* 172:253-261; Tanaka *et al.* (2000) *AIDS* 14:1299-1307; and Juffermans *et al.* (2000) *Blood* 96:2649-2654. Accordingly, based on the current knowledge in the field summarized above regarding the potential role of A_1 adenosine receptors in HIV infection (e.g., in HIV antigen presentation, HIV entry, and HIV replication in macrophages, etc.) and in other immunodeficiency diseases, the skilled artisan would not view the claims as lacking enablement

Similarly, research supports a significant role for P_{2X} purinoceptors in immunodeficiency diseases, including HIV infection, AIDS, and ADA SCID. P_{2X} purinoceptors are expressed on human immune cells such as dendritic cells, macrophages, and T cells and are involved in antigen presentation (e.g., on dendritic cells), cell-to-cell communication and fusion (e.g., via macrophages), and cytotoxicity and apoptosis (e.g., via T cells). See Di Virgilio *et al.* (2001) *Blood* 97:587-600; Apasov *et al.* (1995) *Immunol. Rev.* 146:5-19; and Coutinho-Silva *et al.* (1999) *Am. J. Physiol.* 276:C1139-C1147. Furthermore, as described above, LPS activates nuclear translocation of NF-κB and stimulates expression of HIV in monocytes and macrophages. This LPS-induced activation of NF-κB and the resultant cellular signaling events is inhibited by P_{2X} purinoceptor antagonists, strongly supporting the involvement of P_{2X} purinoceptors in immunodeficiency diseases. See Guerra *et al.* (2003) *J. Endotoxin Res.* 9:256-263. Copies of all of the above references are submitted herewith in the Appendix for the Examiner's consideration.

At points 4 and 5 of the enablement rejection, the Examiner has rejected the claims for failure to provide working examples of the claimed invention. In accordance with the applicable case law, in particular *In re Wands*, however, the presence or absence of working examples is only one factor to be considered in determining enablement. Establishing enablement is a multi-factorial analysis. Accordingly, the Examiner's reliance on the presence or absence of working examples is inappropriate.

The Examiner further remarks at point 8 that "[t]he disclosure fails to provide sufficient guidance pertaining to the structures and binding activities of different A_1 adenosine receptor antagonistic antibodies or P_{2X} purinoceptor antagonistic antibodies." Contrary to the Examiner's assertions, methods for making, isolating, and analyzing antibodies to protein targets such as the A_1 adenosine receptor or the P_{2X} purinoceptor are well known to the skilled artisan and are were provided in numerous references at the time the present application was filed. In view of the knowledge in the art regarding the structure and production of antibodies to a target of interest, Applicant respectfully disagrees with the Examiner's assertions at point 8. Moreover, Applicant maintains that one of skill in the art would be able to readily make and use the recited antibodies without undue experimentation.

Therefore, in light of the above remarks and the knowledge in the art (as evidenced by, for example, the submitted references), a person of skill in the art would conclude that the amended claims are fully enabled. Applicant respectfully requests that the rejection of claims for lack of enablement be withdrawn. Furthermore, because new claims 23-28 depend from claim 1 or claim 5 and additionally recite a single immune system disorder to be treated or prevented (i.e., HIV infection, AIDS, or ADA SCID), Applicant requests that the present rejections not be applied to the newly submitted claims.

CONCLUSION

The Examiner is respectfully requested to withdraw the rejection of the claims and to not apply these rejections to newly submitted claims 23-28. In view of the above remarks and the

claim amendments, it is submitted that this application is now ready for allowance. Early notice to this effect is solicited.

If in the opinion of the Examiner a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

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Pamela Lockley